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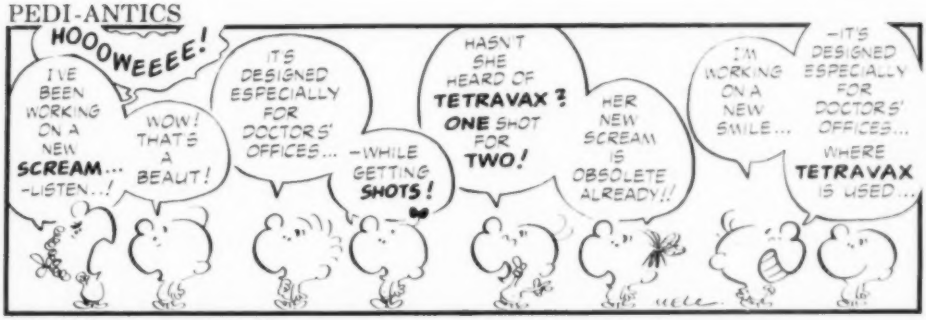
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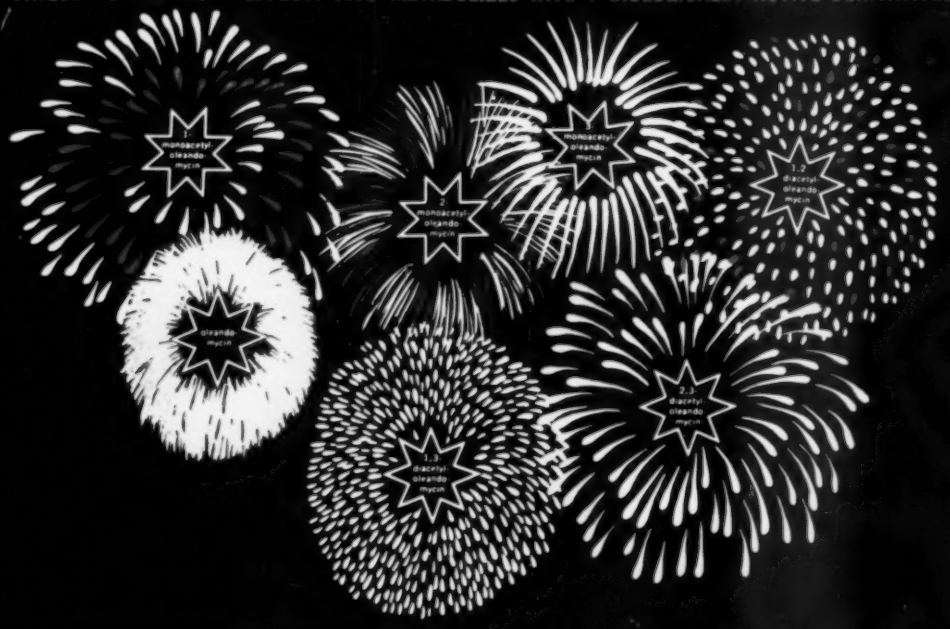

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1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. **100**:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. **8**:420 (Aug.) 1958.

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Lysaught, J. N., and Cleaver, W.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959 (published Nov., 1959)

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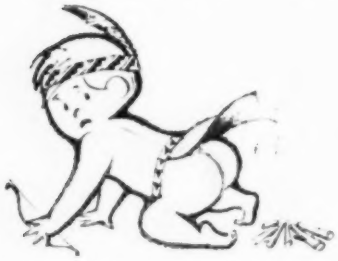

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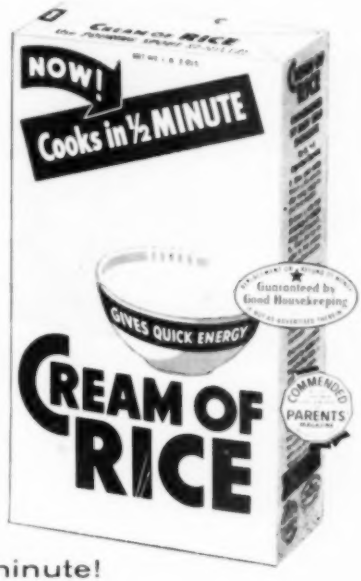

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Pathogenesis of Nodular Atrophy of the Cerebral Cortex*†‡

A Common Cortical Change Found in Cases of Cerebral Palsy

CYRIL B. COURVILLE, M.D.

CALIFORNIA

A survey of the residual cerebral cortical lesions in individuals afflicted with cerebral palsy paralysis dating from birth, suggests that there are two separate processes at work in their production. The first of these processes is a more or less generalized one, affecting particularly the upper portions of the cerebral hemispheres and characterized by a laminar type of cortical degeneration. This regressive change ranges from a loss of nerve cells of laminar distribution on one hand to subtotal destruction of the intermediate cortical layers (lamina III to VI) on the other. These changes roughly parallel a hierarchy of gross lesions ranging from a mild but uniform cerebral atrophy to a widespread cortical softening or sclerotic atrophy. The etiological and pathogenetic significance of this uniform type of cortical atrophy, suggesting a general impairment of the circulation (anoxemia in its broadest sense), was a subject of a previous study recently published (Courville).[1]

By way of contrast, the second pathological process usually produces a more localized and more variegated change in the cerebral cortex. This irregular and often circumscribed atrophy suggests *per se* that the causative factor has acted through some regional mechanism. Nodular cortical atrophy, otherwise known as granular or parchment atrophy or mantle sclerosis, with its attendant structural changes, is the classical prototype of this second process. It is proposed to define and delimit the lesion, to give a brief review of its medical history, to propose an anatomical classification, to take note of certain associated cerebral lesions, to analyze the re-

* From the Cecil Laboratory of Neuropathology, Los Angeles County Hospital, and the Division of Nervous Diseases, College of Medical Evangelists, Los Angeles, California.

† This study was supported by a grant (B-1248), National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

‡ Read before the annual meeting of the American Neurological Association June 16-18, 1958, at Atlantic City, New Jersey.

sultant lesion complexes in terms of their possible pathogenesis, and finally, to draw some conclusions as to their possible etiology.

NODULAR CORTICAL ATROPHY AS A PATHOLOGICAL ENTITY

There is little need to advance any major argument that nodular cortical atrophy is a pathological entity. While different portions of a given cerebral convolution usually present normal variations in its width (as viewed superficially), or in its diameter (as noted on cross section), any transition between these variations occur gradually and smoothly and its internal architecture is unmarked by any irregularities. *Per contra*, nodular cortical atrophy is characterized by wide and often abrupt differences in the width and altitude as well as in variations in contour of a given gyrus (i.e., a mushroom gyrus). Moreover, close inspection of cross sections of a given segment reveal focal variations in the form of clear (acellular) foci and the occurrence of small cysts or irregular scars. These variations become even more conspicuous when one studies, either with the unaided eye or hand lens, a portion of cortex stained by certain special methods (Nissl, myelin sheath, reduced silver, or Perdrau).

Nodular cortical atrophy can therefore be defined as an irregular shrinkage or atrophy of the cerebral cortex, evidently the result of parenchymatous damage and accounting for either focal necrosis or sclerosis of more seriously affected regions. Associated lesions of the underlying white matter in the form of demyelination or cyst formation, are probably secondary. Although in this connection one is concerned with changes dating back to birth or early infancy, quite similar lesions are also to be found occasionally in the brains of older individuals. Such lesions have been described under other names in the French (état vermoulou) and German literature (Schizogyrie). This fact alone should serve to prove that nodular cortical atrophy is not a disease but the end-result of a pathological process. This lesion has a long and somewhat involved history which extends from the time of Cruveilhier to the present, a brief review of which will lay a solid foundation for a comprehensive study of its pathogenesis and exciting cause.

MEDICAL HISTORY OF NODULAR CORTICAL ATROPHY

The historical aspects of the problem may be divided into three periods: (*1*) identification of the lesion, (*2*) development of concepts about its nature and (*3*) conjectures regarding its etiology.

The earliest references which seem to deal with this lesion are not always clear in their precise implications. Breschet[2] and Abercrombie[3] seem to be the first to make note of it. Pinel the Younger is also credited by Schob as describing it. However, Cruveilhier[4] not only gives a case report of the lesion found at autopsy in a mentally retarded child (Plate VI, Book VIII) but also clearly depicts it in one of his lithographs (fig. 1). In addition, he applied a specific name to it (*induration cartilagineuse*) which characterizes it in a graphic manner. Other terms appearing in the literature of this period are equally suggestive ("Induration of a portion of the brain" [Carlile[5] 1841]; "induration limitée des circonvolutions cérébrales" [Dufour[6] 1851]; "Sclerosi cerebri partiali [Wintzer[7] 1862]), although the original texts of these papers were not available for a critical evaluation of the lesion.

Fig. 1. Typical historical example of nodular cortical atrophy (central type of lobar sclerosis of left cerebral hemisphere) as depicted in a lithograph in Cruveilhier's Atlas (Anatomie pathologique du corps humaine, 1829-1842).

As time went on, various reporters who dealt with this lesion continued to contribute to its morbid anatomy as well as its clinical aspects. Cotard[8] was among the first to deal with the problem of cerebral cortical atrophies as a whole. Binswanger[9] noted specifically its isolated occurrence in an atrophic cerebral hemisphere. Its presence as the apparent causative lesion in cases of idiocy associated with paralysis was also observed by Major[10] and Chiari[11] ("partial microgyria"), and other contributors in the next two decades (i.e., Kaes,[12] Kast,[13] Schutte,[14] and Wachsmuth[15]). Its significance as a cause of epilepsy, as well as idiocy, was also mentioned (Major,[10] Bourneville[16]). Meanwhile, Heschl[17] published a small monograph on this type of cortical atrophy, and is credited by some with the recognition of microgyria as a specific lesion.

Other contributors pointed to the localization of this change to circumscribed areas of the brain (Jendrassik and Marie,[18] Otto,[19] Bresler,[20] Zingerle[21]) so that the term of "lobar sclerosis" was adopted for it.*

The problem of the pathogenesis of nodular cortical atrophy has received attention from most contributors of major essays on this subject. Not all have come to specific conclusions, but of the many different concepts proposed, a wide divergence in their etiology has been implied. Inflammation of one sort or another was considered as the essential cause by some (encephalitis [Ganghofner[22] and Binswanger[23]]; "chronic interstitial inflammation" [Schmaus[24]]; meningitis [Bresler[20]], and possibly syphilis [Greiff,[25] Collier[26]]). Vascular disorders of one type or another were believed to be the chief etiological factor by others (subarachnoid hemorrhage [McNutt[27]]; subdural hemorrhage or hematoma [Koppen[28]]; thrombosis of venous channels [Gowers[31]]; thrombosis of a major artery [Kast,[13] Freud[32]]) or a disease of the small blood vessels (Jendrassik and Marie[18]). Some investigators considered the disease to be a degenerative disorder (Wernicke,[33] and Collier,[26] and Campbell[34]). The association of lobar sclerosis with the birth process was believed to be significant by still another group (prematurity [Brissaud[35]]; birth trauma [Oppenheim[36]]). It is of interest to note that Wachsmuth[15] fostered the idea that paranatal asphyxia had something to do with its genesis. Of these various possible causes, the concept of vascular occlusion has finally come to be favored by most modern students of the problem. Most of these have inclined to the idea of thrombosis of the superior longitudinal sinus and its afferent veins (i.e., Hallervorden),[37] but a few conclude the lesion to be the result of arterial occlusion (i.e. Spatz)[38] because of its resemblance to similar lesions in elderly people. Some evidently believe that either mechanism can be responsible for the condition (Benda,[39] Norman *et al*[40]). A recent contribution (Morel and Wildi[41]) described nodular cortical atrophy under the term *dysgénésie nodulaire disséminée* reporting its occurrence in a series of 25 cases which includes both its natal and senile forms.

* It was about this time that the clinical term of "cerebral diplegia" or Little's disease came into vogue in describing children afflicted with spastic paraplegia (Massalongo,[29] Collier[26]). When the lesion causing this condition was verified at autopsy, it was found to be either a localized collection of atrophic gyri in the upper central region or a porencephalic defect. When the two lesions were found to be associated, porencephaly was considered to be a more advanced stage of the same pathogenic process (Salaz[30]).

PATHOLOGY OF NODULAR CORTICAL ATROPHY BASED ON PERSONALLY STUDIED MATERIAL

What may seem to be a heterogeneous group of atrophic cortical lesions, judging from occasional cases, can actually be divided, on the basis of their distribution, into several fairly well-defined subgroups. The finer anatomical changes in these different groups are found to vary considerably. These variations in distribution and structure soon become quite apparent when a larger group of lesions found at autopsy becomes available for survey.

Material for study.—The cases in which this lesion occurred (40 in all) were separated from a larger group of 155 cases. The individuals had been afflicted with cerebral palsy, mental deficiency and epilepsy alone or in combination of these states which dated back into early life, presumably from birth. In all cases, the cerebral lesion was verified at autopsy giving full opportunity to study the nature, size and distribution of individual lesions. The distribution of the lesions in nodular cortical atrophy in the 40 cases cited is indicated in the following table (Table I).

TABLE I

Anatomic Distribution of Nodular Cortical Atrophy

I.	Isolated gyral atrophy		4 cases
	A. Solitary	3 cases	
	B. Multiple	1 case	
II.	Lobar sclerosis		6 cases
	A. Frontal group	3 cases	
	B. Parieto-occipital group	3 cases	
III.	Massive central cortical sclerosis		7 cases
	A. Unilateral	2 cases	
	B. Bilateral	5 cases	
IV.	Microgyria associated with porencephaly		13 cases
	A. Adjacent and incidental to cyst	6 cases	
	B. As a separate lesion	7 cases	
V.	Medial frontal group		4 cases
VI.	Medial occipital group		0 cases
VII.	Multiple foci, symmetrical or asymmetrical		5 cases
VIII.	Generalized nodular atrophy		0 cases
IX.	Hemispheral nodular atrophy		0 cases
X.	Lesions of irregular distribution		1 case
		TOTAL	40 cases

DISTRIBUTION OF LESIONS

A survey of the pertinent literature makes it clear that students of the problem have already recognized considerable variation in

the location of the lesion. In addition to numerous examples of so-called lobar sclerosis, bilateral lesions were also described by early writers (Salgo,[21] Otto,[19] Köppen[42]). Bourneville[16] was one of the first to recognize this variability in localization and distinguished cases in which the entire cortex of one or both cerebral hemispheres appeared to be affected, as well as atrophy of a single gyrus or lobe. More recent contributors (Schob,[43] Josephy,[44] Malamud[45]) who must have had more experience with such lesions, seem content to mention only the localized and generalized types. Benda[46] for example, notes that "The condition may affect parts of one lobe or a whole lobe or even one hemisphere. The condition is asymmetrical or may be bilateral." However, the present writer has encountered no instances other than the primary or "congenital type" of the disorder in which either one or both entire cerebral hemispheres have been affected.

Based on his series of 40 cases, as well as those reported in the literature, the present writer has been able to separate the cases on the basis of distribution as follows: (1) isolated convolutional lesions often located in the upper central areas,* (2) lesions limited to a single lobe (lobar sclerosis of Bresler), usually the frontal or parieto-occipital region, (3) extensive central lesions, usually bilateral and symmetrical in location, (4) secondary microgyria associated with porencephalic cysts, (5) medial frontal lesions, (6) medial occipital lesions, (7) multiple lesions affecting symmetrically both cerebral hemispheres, (8) multiple, irregularly distributed foci of atrophy as well as two hypothetical groups, (9) hemispheral nodular atrophy, and (10) generalized nodular atrophy.

Isolated Atrophic Gyri.—This type of lesion is frequently found as a surgical lesion in focal epilepsy. Because of its minor character, it can be readily overlooked even on autopsy. As anticipated, the altered convolution is irregularly narrowed and may be localized in a depression between two normal or even larger than average gyri. The true nature of this alteration may thus be missed unless the brain section passes through the altered gyrus at right angles. At times, close inspection will disclose more than one focus of these atrophic convolutions (fig. 2-A). Since in the writer's experience this change affects most often the upper portion of the

*Sarasohn sometimes expose what are called focal scars or cortical cysts as epileptogenic lesions (Ford,[47] Penfield and Erickson[48]). These scars usually prove to be isolated atrophic and sometimes sclerotic gyri, sometimes associated with cortical cysts. A review of the histological structure of these lesions proves them to be essentially identical with these isolated atrophic convolutions.

pre- and postcentral gyri, a coronal section at this level may fail to demonstrate it clearly unless other cuts are made at right angles. Typically, these upper central lesions should occur in cases of spastic paraplegia (Little's disease).

Lobar Sclerosis.—It is this anatomic type of nodular cortical atrophy, which is best known. It has come to be so designated since described by Bresler,[20] although the lesion had been recognized by others before him (Jendrassik and Marie[18]; Bourneville[16]). The last named contributor in particular considered it to be only one of a group of variously distributed lesions. This localized form of cortical atrophy is limited either to a single lobe or involves adjacent portions of two lobes. In this connection we are limiting the lesion to the dorsolateral aspect of the frontal and/or the parieto-occipital cortex. In the frontal region the individual convolutions are usually but not excessively narrowed (fig. 2-B), while in the parieto-occipital area they may be reduced to small closely-packed worm-like ridges.

The possibility of symmetrical areas of both cerebral hemispheres being affected by nodular cortical atrophy has long been recognized (Kast,[13] Salgo,[21] Otto,[19] Köppen, 1895,[12] 1897,[10] 1898[30]). These bilateral lesions may be present on the dorsolateral surfaces of both occipital lobes (probably more often) or the same surface of both frontal lobes. At times the symmetrical lesions may be elsewhere (both upper central regions, medial aspects of both hemispheres with changes in the cortex of the paracentral lobule). Less commonly, bilaterally symmetrical foci will be found in double, rarely in triple symmetrical foci.

Extensive Central (Frontoparietal) Lesions.—On a critical analysis of the individual lesions it was somewhat surprising to find a fairly large group of cases in which nodular cortical sclerosis affected the midportion of the dorsolateral central (frontoparietal) cortex (fig. 2-C). The lesion was bilateral in all but one case of the writer's series. The exact conformation of the area of altered cortex, as well as its size, often varies in the two hemispheres. The degree of change may also be more advanced in one hemisphere than in the other, although it was often quite similar on both sides. These obviously advanced lesions probably account for an early death in individuals so affected, for it is rare for patients with large bilateral lesion, to survive beyond the age of 3 years. It is pertinent

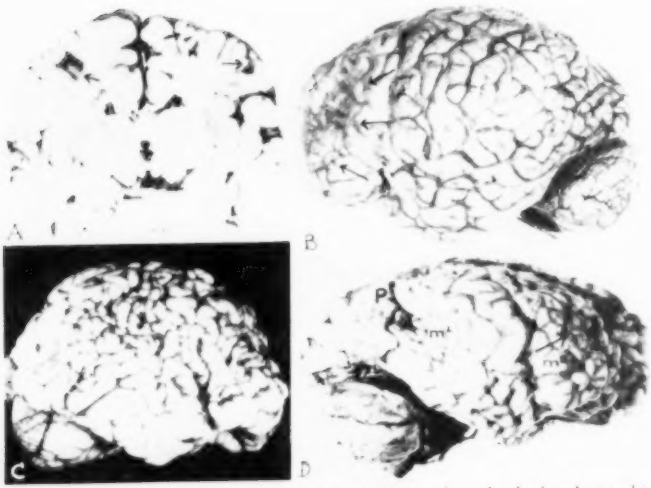

Fig. 2.—Anatomical types of nodular cortical atrophy. A, Isolated atrophic gyri. Note shrunken convolutions in various portions of the cerebral cortex (arrows). B, Lobar sclerosis (ulegyria). The individual convolutions of the left frontal lobe are irregularly shrunken (arrows) causing atrophy of the entire lobe. C, Central (frontoparietal) nodular atrophy. Irregular atrophy of the posterior frontal, pre- and postcentral and inferior parietal convolutions. Note apparent increase in size of the right temporal lobe. D, Microgyria associated with porencephalic defect. P, porencephalic cleft in right parietal region. m', microgyria at margin of defect. m'', isolated group of atrophic gyri in right frontal lobe. Note unusually large right precentral gyrus ("compensatory hypertrophy").

to point out that the affected cortex in this group falls within the area supplied by the middle cerebral artery.

Nodular Atrophy Associated with Porencephalic Defects.—This group of cases is placed at this point in the classification because the location of the porencephalic defects strongly suggests a total occlusion in early life, the late intrauterine, paranatal or early postnatal periods of the middle or other cerebral arteries or one of their branches. This would tend to confirm the conclusion of Salgo,[24] and Koppen[42] that a porencephalic defect is actually a most severe degree of regressive change of which nodular atrophy is the most minor. The association of atrophic convolutions with porencephalic defects has been noted by a number of early contributors to this subject (Chiari,[11] Binswanger,[30] Anton,[31] Otto,[19] Muratoff,[32] von Kahlden,[33] Schutte[14]).

On the basis of the writer's material, it seems advisable to subdivide these cases into two groups. In the first, the atrophic con-

volutions are but part and parcel of the porencephalic defect and suggestively due to the same mechanism. The second subgroup is characterized by the presence of atrophic gyri as a separate and distinct lesion (fig. 2 D) from the porencephalic defect. This can only mean that multiple areas of the brain were being subjected, more or less simultaneously, to ischemic change.

Medial Frontal Group.—In a few cases, the atrophic gyri were located on the medial surface of the cerebral hemispheres (fig. 3-A). This focus usually corresponds to the paracentral lobule,

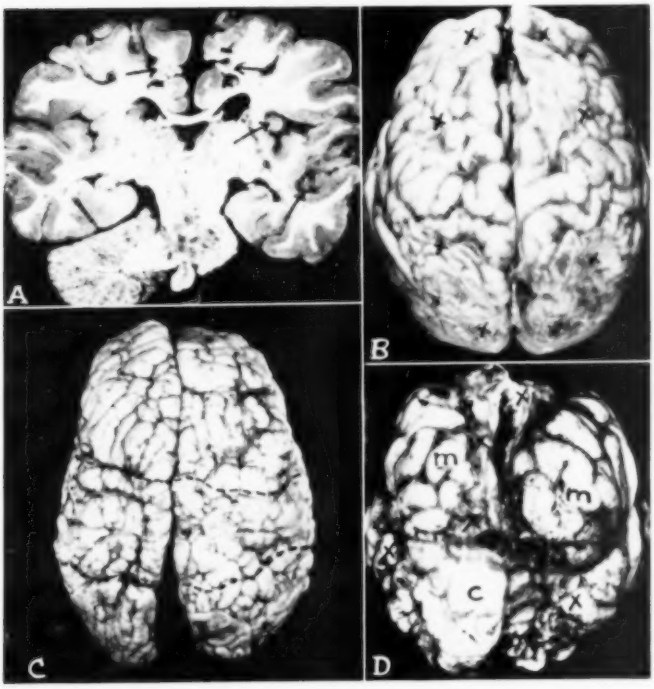

Fig. 3. Anatomical types of nodular cortical atrophy (continued). A. Focal nodular atrophy of medial surface of both cerebral hemispheres (arrows). Focal atrophy is also found in convolutions bordering left sylvian fissure. B. Multiple symmetrical foci of microgyria in frontal and parieto-occipital regions. Note comparative enlargement ("compensatory hypertrophy") of prefrontal convolutions, especially on the left. C. Example of mild nodular cortical atrophy which seems to be generalized but which actually affects essentially the central areas as indicated by the dotted lines. D. Irregular distribution of areas of nodular cortical atrophy (x) associated with cortical-subcortical cyst formation (c) and macrogyria (m).

lying within the area of distribution of the anterior cerebral artery. In this series, the lesion was bilateral although the possibility of a unilateral focus of atrophy must be acknowledged.

Medial Occipital Group.—The writer has seen no well-defined isolated *medial* occipital foci of cortical atrophy of this type, nor does he recall any reported cases. Yet this possibility must be recognized as an atypical example would indicate.

Multiple Symmetrical Foci.—In addition to bilateral examples of lobar atrophy and of extensive central nodular atrophy, occasional examples of bilateral and multiple symmetrical foci are also encountered. In these cases the pattern varies from one case to another as to the precise location of individual lesions. Examples of dorsolateral or medial frontal, central, parietal or parieto-occipital lesions may be found (fig. 3-B). The only conclusion that can be drawn in these instances is that some noxious influence affecting symmetrical branches of both middle and or anterior cerebral arteries was at work.

Multiple Foci of Microgyria of Irregular Distribution.—Oddly enough, multiple lesions of grossly irregular distribution seem not to be very common in this type of cerebral cortical atrophy. This in itself may ultimately prove to be significant. In the one case in the writer's series, the brain was remarkably deformed with irregularly distributed foci of nodular atrophy interspersed with compensatory macrogyria on one hand and areas of total softening and cortical-subcortical cyst formation on the other (fig. 3-C).

Hemispheral Nodular Atrophy.—Atrophic changes in all of the convolutions of one cerebral hemisphere are implied in reports of early observers such as Bourneville[18] and Zingerle.[21] The present writer has seen no such case, nor do any of the illustrations of reported cases of the so-called secondary type of this disorder seem to bear this out. This, however, seems to be definitely possible in primary (congenital) cases of microgyria. In what might seem to be true hemispheral examples, close inspection seems to show that the medial surface of the hemisphere and/or the area supplied by the posterior cerebral artery (if not of carotid origin) are not involved in the process.

Generalized Nodular Atrophy.—Attention has already been called to the fact that this particular type of cortical change may be so extensive as to involve apparently the entire cerebral cortex

(Bourneville,[16] Zingerle[21]). This conclusion has been echoed by practically all subsequent students of the problem. Whether these examples are limited purely to the "primary" or congenital type, as the present writer has come to suspect, or whether some *bona fide* cases of the secondary variety may also occur is not yet clearly established. In one of the writer's cases, at first considered to be a generalized example of the lesion, critical inspection of the distribution of atrophy indicated that it was found chiefly in the distribution of the middle cerebral artery (fig. 3-D).

DETAILS OF CORTICAL CHANGE

No consideration of the pathology of nodular cortical necrosis would be complete without some attention being given to the essential nature of this change. It is quite clear that there is not only a wide difference in the degree and nature of atrophy from one case to another, but also with respect to the relation of this change to the stage of development of the convolutions affected thereby. Some convolutions had obviously attained a considerable degree of maturity prior to the onset of atrophic change. In others, the altered gyri are just as obviously immature, the process of atrophy having begun at a relatively early period in cortical morphogenesis. This has led to the rise of the term of *primary* or *congenital* microgyria.

Primary Microgyria.—There is occasionally reported a case of microgyria (schizogyria) in which the highly complex atrophic convolutions are quite sharply circumscribed. The very nature of the lesion implies a rather stable structure which in turn suggests its original slow evolution and present relative quiescence. Such a complex has been designated by some as a *primary* or *congenital microgyria*. This state is not to be confused, however, with the so-called *microgyria verrucosa* in cases of congenital hydrocephalus in which the only architectural alterations (i.e., heterotopia) are themselves obviously congenital. Its similarities to the lesion here considered raises the question as to whether or not the primary type is also the result of a partial ischemia *in utero* occurring at an earlier stage of development. An usual variety of these primary cases have been described by a number of contributors such as Jacob,[34,35] Binswanger,[59] Benda,[46] Peters,[56] and Malamud.[45] In these instances, what seems to be a superimposition of nodulation of the cortical gray matter upon either a congenitally small convolution (macrogyria in case of Benda[46] ["Loaf of bread brain"] or an

atypical arrangement of the convolutions (as in case of Peters[28] and Malamud[16]). It seems almost certain, on this basis, that one is not here concerned with a "pure" congenital defect but rather a combination of a primary and secondary lesion. Because this type of change seen in some cases of primary porencephaly (the so-called schizencephaly) with which microgyria is so often associated, the possible ischemic origin of such finer cortical changes seems to be plausible. This primary type of cortical atrophy was found in only one case of our series (superimposed on a mild macrogyria) so that at present the writer is unable to substantiate his theory in this respect. This entire problem demands further critical study before it can be considered as settled.

In a consideration of the nature of nodular cortical atrophy, one must recognize several different degrees of alteration. Beginning with the simplest and least changed cortex, the resultant alteration might be named (1) the bulbous or "mushroom" gyrus formation. (2) Verniform atrophy consists of a cluster of convolutions which are markedly atrophic but in which nodulation is not particularly conspicuous. (3) Nodular or granular atrophy, on the other hand, is marked by irregular cortical scars of which a number of degrees can be distinguished. Another more advanced lesion (4) atrophic sclerosis, is one in which a process of irregular sclerosis in which the cortex has lost most of its parenchymatous elements with a replacement gliosis. (5) Cortical cyst formation seems to be a characteristic of still other cases in which necrotic material in the intermediate laminae have been removed. In occasional examples, (6) small convolutions of this type are found to be undergoing an irregular subtotal softening.

Bulbous ("Mushroom") Gyri.—This type of alteration takes its name from the contour of an individual gyrus as seen on cross section (fig. 4 *A*). The crown of the convolution seems to have a normal contour, although actually its population of nerve cells may be considerably decreased. The cortex of the lateral aspects of the gyrus, on the other hand, is appreciably narrowed, being reduced at times to a very thin zone of translucent gray matter. This change is accentuated by a dilatation of the bordering sulci. The altered segment is often quite sharply delineated from surrounding normal cortex. The fact that the sides of the gyrus are more vulnerable to ischemia suggests that this is the probable mechanism of its production.

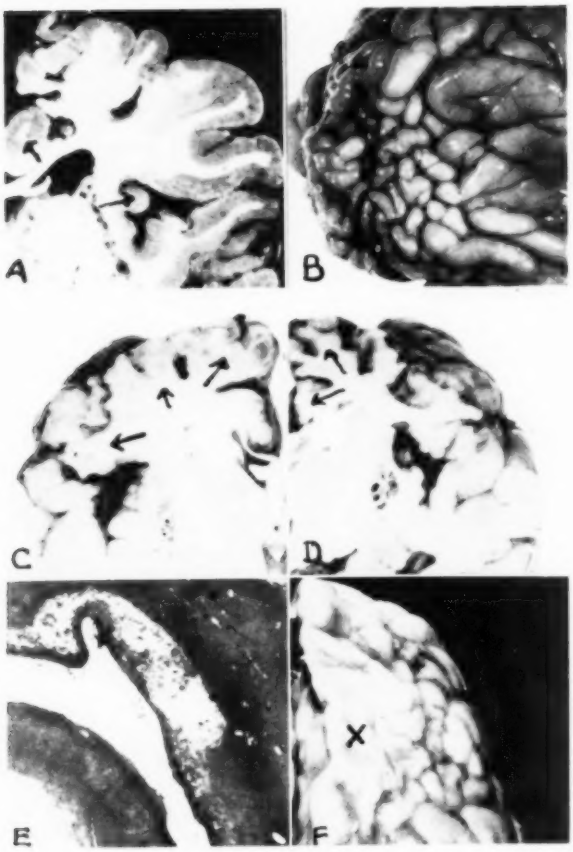

Fig. 4. Structural types of nodular cortical atrophy. A. Bulbous ("mushroom") convolutions (arrows). B. Vermiform atrophy. C. Typical nodular or granular atrophy. D. Sclerotic atrophy. E. Cortical cystic degeneration. F. Cortical softening (X) associated with microgyria.

Vermiform Atrophy. This type of cortical atrophy is usually included under the term of mantle or nodular sclerosis although, in a strict sense, the involved convolutions are quite uniformly reduced in size and have not undergone sclerosis. But when seen in a cluster, particularly in cases of lobar atrophy, the first impression is that of a nodular type of shrinkage. In fact, however, the lesion consists of an increased number of convolutions of unusually small

size but of quite uniform diameter (fig. 4-B). This characteristic suggests its origin in some antenatal disturbance in the circulation of the affected region.

Nodular (Granular) Atrophy.—This form of atrophy represents the type lesion of the group (fig. 4-C). As the term implies, the atrophic cortex has an irregularly nodular or even a finely granular conformation. By implication, the size of the individual nodules would be proportionate to the size of the arteries affected by the ischemic process. This type of change is shown up particularly well in cross section and in sections stained by Nissl's method or impregnated by Cajal's reduced silver method. These methods make it clear that the nodulations consist of better preserved masses of cortical gray matter, with intervening constrictions composed of gliotic and vascular scars resulting from a focalized ischemia.*

Irregular Sclerosis. This type of atrophy differs from the previous one only in its less obvious nodulation and more profound degree of replacement gliosis (fig. 4-D). It is closely allied with, in fact a local variant of, the so-called "walnut kernel" brain, which differs from the cortical alterations in the type here considered by the less uniform degree of atrophy and by a more or less universal gliosis. What seems to be a classical example of this condition is depicted by Malamud in his Atlas.[45] In the bordering regions, fairly typical nodular atrophy may be seen. The cortical changes are obviously secondary to the process of slow ischemia.

Cortical Cyst Formation (Cortical cystic degeneration [Malamud][45]).—A modification of nodular sclerosis occurs in some cases in which it is possible to see, even with the unaided eye, the presence of numerous small cystic spaces within the cortex itself (fig. 4-E). This is visualized only on cut sections of the cortex. The cortical irregularities in such cases are evidently due, not so much to a preservation of the parenchyria, but rather to the presence of clusters of these cysts which actually widen the cortex. The greater number of cysts in a given region, the wider the cortical ribbon. This process may well be an exaggeration of the change described as status spongiosus. Cortical cystic degeneration tends to occur in areas of the cortex which are undergoing softening and

*A contemporary study by the writer (Dustman, cerebral cortical circulation and local vascular lesions) may be profitably consulted for additional light on this process of irregular cortical atrophy and should be referred to by any reader interested in pursuing this subject further.

adjacent to cortical areas which show profound degrees of softening (Malamud[25]). Areas of gliosis intersperse these small cysts.

Softening in Atrophic Gyri.—In rare instances, one finds what seems to be a slowly progressive softening of convolutions which are already atrophic (fig. 4-F). Whether a more acute regressive change is superimposed upon a cluster of convolutions already atrophic by an ischemic process or whether the two types of changes are taking place simultaneously, is uncertain. Benda[16] has depicted an excellent example of this lesion.

These observations serve to emphasize the complexity of what was once thought to be a single type of nodular cortical atrophy. It is evident that one has to do with a lesion-complex whose kaleidoscopic aspects may even be more confusing than its apparent etiology. But still another feature which tends to complicate the picture (although it may also help solve the matter of its genesis) is that of a variety of not uncommon associated lesions.

ASSOCIATED LESIONS

Associated physical changes found in the cerebral hemispheres in relation to nodular atrophy also merit attention. In some cases, nodular atrophy occurs in the cortex of hemispheres covered by a neomembrane, the remains of an old subdural hematoma. Particularly noteworthy also is the presence in a goodly number of specimens of porencephaly. The occurrence of unusually large convolutions (compensatory macrogyria) especially in the margin of the altered cortical area is at times conspicuous. Cortical softening or cortical-subcortical cyst formation are less common associated lesions. Regional demyelination and/or cyst formation in the subcortical white matter also needs to be considered. Cystic degeneration of the cerebral white matter, at times quite extensive, is found in a few instances. Alterations in the basal ganglia in the form of diffuse cell loss with gross atrophy of the nuclear mass, actual necrosis or status marmoratus may also occur. It is pertinent to discuss this group of associated lesions at this time.

Subdural Hematoma. Old unilateral or bilateral subdural hematomas have been noted in connection with nodular cortical atrophy (Köppen,[30] Schmincke[28]). It may well be that this association suggested to earlier writers that trauma at birth was responsible for the atrophic changes in the cortex. In the writer's experience, the most marked atrophic changes were found in the motor cortex of

the cerebral hemispheres, beneath and partially obscured by the hematoma. This raises the question as to whether the cortical change is actually due to pressure by the overlying hematoma. The fact that this type of cortical atrophy usually occurs without a covering hematoma, and the fact that actual softening of the cortex is a more likely residual in subdural hematomas of infancy (Phillips[59]) would favor the occurrence of some other etiological factor.

Nodular Atrophy and Porencephaly. Many of the early writers have commented on the association of nodular cortical atrophy and porencephalic defects (Binswanger,[30] Anton,[31] Muratoff,[32] von Kahlden,[33] Koppen,[34] and Siegmund[60]). In the writer's series, this association was noted in 13 of 40 cases (32.5 per cent), too often not to have some significance. In six of these cases, nodular cortical atrophy occurred in parts of the hemispheres other than in the immediate vicinity of the porencephalic defect. In either case, it is reasonable to conclude that both lesions are the result of a similar if not identical process.

"Compensatory Hypertrophy" of Regional Convolutions. About the margins of areas of nodular sclerosis, one sometimes finds unusually large convolutions. The magnitude of these convolutions is often proportional to the severity of general cerebral atrophy, suggesting that this hypertrophy is in a sense "compensatory". When a group of gyri fail to develop, any restraint on adjacent convolutions is removed and the unaltered structures attain a larger than normal size.

Cortical-subcortical Softening and Cyst Formation. Occasionally one finds certain areas of the cortex and underlying white matter which have undergone a degree of actual softening. These areas are not infrequently adjacent to areas of nodular atrophy. The degree of softening may vary considerably, being so minor as to be scarcely evident, or so marked that the cortical gray matter is completely disintegrated. This change was noted in three specimens studied by the writer, being unusually prominent in one. In two other cases circumscribed cortical-subcortical cysts were found in association with chronically altered cortex.

Regional Subcortical Demyelination and/or Cyst Formation. Whenever the cortical change is quite marked and sharply circumscribed, the underlying white matter usually shows some degree of demyelination. This is obviously secondary to the wholesale loss of efferent axons incident to death of cortical nerve cells. Cyst forma-

tion (the cysts are usually quite small and variable in size) evidently represents a similar but more rapidly developing lesion.

Cystic Degeneration of the Cerebral Centrum. This usually widespread degeneration of the cerebral white matter is quite a different process than the one described in the foregoing section. It has long been described as "central cystic degeneration" and is an entirely different lesion. Most, if not all the cerebral white matter is transformed into large intercommunicating cavities. The overlying cerebral cortex may be grossly normal; may be considerably thinned; or show a considerable extent of nodular atrophy. The association of these two ordinarily independent lesions speaks for a similar, if not identical pathogenic process. Cerebral cystic degeneration seems to occur in cases of nodular cortical atrophy only this latter change is quite widespread.

Alterations in the Basal Ganglia. Changes in the basal ganglia (corpus striatum, globus pallidus and thalamus of one or both hemispheres) are usually not conspicuous. Such changes may occur, however, in one of three forms which are evident grossly, (1) atrophy of the nuclear mass due to a chronically progressive deterioration of the resident nerve cells, (2) status marmoratus or dysmyelinsatus, or (3) gross necrosis leading to formation of a single large, or multiple small cysts. The most common of these changes seems to be atrophy *in toto* of one or more of these nuclear masses. However, in cases of cleancut examples of status marmoratus, foci of nodular cortical atrophy may indeed occur, at times as a less conspicuous process. In these cases, there seems to be an increased prominence of myelinated nerve fibers in the cortex as well as in the basal ganglia. In one of the cases in the writer's series, the lenticular nucleus had undergone complete destruction with only a cyst with fairly sharp borders marked with fine hairlike strands remaining.

HISTOPATHOLOGY OF NODULAR CORTICAL ATROPHY

It would take one too far afield to describe in detail the multiform alterations in the architecture and cellular elements in nodular cortical atrophy. This has already been quite well done by other students of the problem (Koppen,[42] Siegmund,[59] Campbell,[24] Schob,[53] and Josephy[44]). Only a brief note will be made of the essential types of change with particular reference to those having a possible bearing on the genesis of the disorder. These details

include the irregular patchy loss of the nerve cells, the formation of irregular glial scars, the significance of status spongiosis and intracortical cyst formation, the formation of "sheaf-of-wheat" bundles of glial fibrils, the alterations in the vascular pattern of the atrophic cortex, and secondary subcortical demyelination.

Parenchymatous Damage.—The characteristic feature of nodular cortical atrophy is an irregular patchy loss of the pyramidal cells. This feature stands out in contrast to the laminar loss of these elements resulting from a diffuse circulatory process (i.e., anoxemia) elsewhere described (Courville[1]). This irregular loss of cells, particularly well demonstrated in reduced silver preparations, gives rise to two contrasting pictures. The first, as already implied, occurs as isolated or fused acellular foci in fairly evenly narrowed stretches of cortex. In more severely damaged areas in which nodulation is more obvious, islands of preserved cells remain in a clearer background of hyalinized stroma. The more profound degrees of parenchymatous degeneration occur in the intermediate laminae of the cortex.

Even in areas that still retain many of their original neuronal elements, serious damage to individual nerve cells is evident. There are regressive changes in the morphology of the cell, as well as alterations in its structure. This occurs as a more or less complete loss of the tigroid substance as well as dissolution of the neurofibrillary network.

Profound alterations in the unmyelinated nerve fibers forming the warp and woof of the cortical structures are also evident. A decrease in number of these elements as well as their varicosity, fragmentation and granular degeneration of their axis cylinders, is evident under higher magnifications. End-bulbs are also to be found.

Reaction of the Interstitial Elements.—The oligodendroglia are not conspicuous in the altered cortex and, judging from their reaction to ischemia under other circumstances, are lost early in the process. Aside from the presence of occasional compound granular corpuscles about the blood vessels, the presence of the unaltered precursor elements, the microglia, is not noteworthy. It is the neuroglia that plays the most conspicuous part in the reaction of the stroma. Proliferation of these elements in the subpial glial layer and their transformation from the protoplasmic to the fibrous

variety give rise to a felt work of glial fibrils which may be very dense.

One interesting and unique formation of glial fibrils is the "sheaf of wheat" bundles observed in the more scarred regions. In some areas these bundles may be conspicuous for their size and number. It is difficult to understand their exact mechanism of formation.

Status Spongiosus and Intracortical Cyst Formation. The occurrence of collections of vacuoles in the cortex are reminiscent of a recent stage of cortical alteration incident to cerebral anoxia. These intracortical cysts may indeed be related to status spongiosis in their pathogenesis but probably an end-stage of the process. In keeping with the more irregular and localized pattern of change in nodular cortical atrophy, the total breakdown of the intermediate laminae tends to form small cysts rather than a widespread separation of the external and internal strata of the cerebral cortex. These cystic spaces are variable in size and extent and tend to form a linear series of cavitations. This cortical complex may present a fusiform contour because the largest cysts often occur in the middle of the series.

Alterations in the Blood Vessels.—In general, two types of vascular change are to be found in the cortex affected by nodular atrophy. The more conspicuous but less common change is characterized by a local proliferation of the vascular endothelium. This gives rise to the occurrence of closely packed blood vessels forming a rather dense scar. This alteration is much more common, however, in the diffuse cortical alterations of the general anoxic process.

The second change may be described as a progressive reduction in number of small blood vessels in the acellular areas. Indeed, it is this reduction of vessels which is probably responsible for the breakdown of the parenchyma. The alterations in the vascular pattern in various stages of nodular cortical atrophy is the subject of further study by the present writer.

Focal Subcortical Cyst Formation and Demyelination.—One rather conspicuous change in the vicinity of a focus of advanced nodular cortical atrophy, albeit a secondary one, is the occurrence of adjacent subcortical cyst formation or demyelination. The fact that this association is also present in focal ischemic atrophy of the cerebral cortex in later life suggests some essential relation between

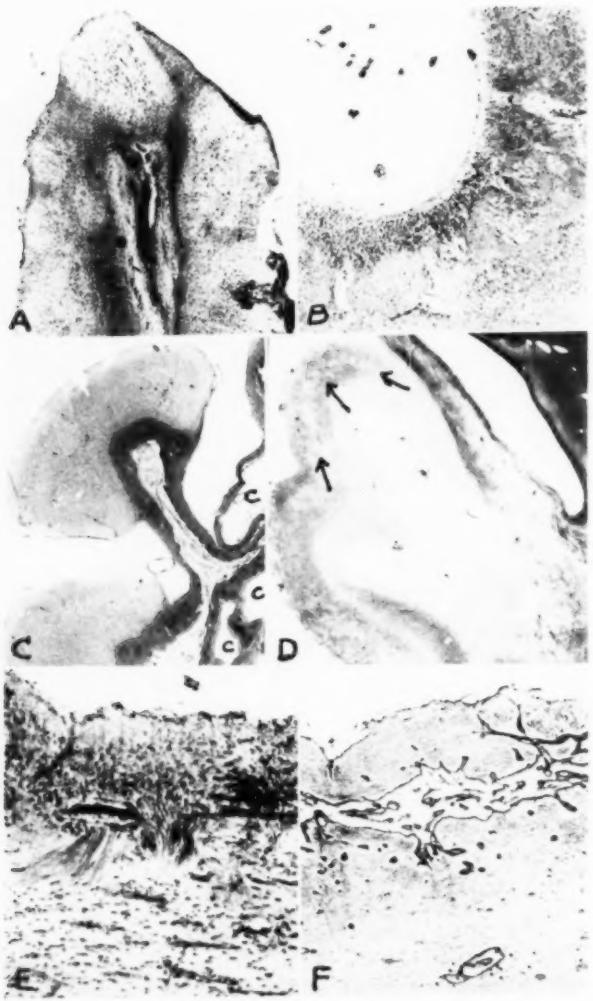

Fig. 5. Histological characteristics of nodular cortical atrophy. A. Patchy loss of nerve cells. Reduced silver. B. Status spongiosus in evenly atrophic cortex. Reduced silver. C. Typical "mushroom" gyrus associated with central cystic degeneration. (c) Central cysts. Reduced silver. D. Zone of laminar necrosis (arrows) with subcortical demyelination and cyst formation. Myelin sheath preparation. E. Sheaf-like bundles of glial fibers in altered cortex. F. Irregular vascularization in mildly atrophic and scarred cortex (defects surrounded by reticulin). Perdrau's method.

these two lesions. The gross aspects of this change have already been considered in a previous section. Cyst formation probably represents the end-result of a more rapidly developing, a more advanced and more extensive lesion. Demyelination is more apt to occur whenever the changes are more focal. Both lesions are due to a degeneration of the axons of corticofugal nerve fibers after the cell body has been destroyed. These changes are noted in figure 5.

PATHOGENESIS OF NODULAR CORTICAL SCLEROSIS

With this background as to the distribution and character of the change generally and collectively described as nodular cortical atrophy, one is prepared to explore the problem of its pathogenesis. There is more to the problem of its total mechanism than to determine the nature of the final act which results in its formation. If it is indeed a vascular lesion, as most writers on the subject now believe, is it of arterial or venous origin? What process sets in motion the circulatory change ultimately responsible for it? At what stage of development is the process initiated? Does the not infrequent occurrence of areas of nodular atrophy in bilaterally symmetrical foci have any meaning? What is the reason back of the variability in nature of the individual lesion? Is there reason to believe that the lesion is a progressive one?

The stage for this discussion has been well set by a recent contribution on the subject of vascular mechanisms at work in birth injury (Norman, Urich and McMenemey).[40] It was pointed out in this review that the venous origin of this type of lesion has long been believed to be the correct one. This theory dates back at least to the contribution of Gowers[31] who considered thrombosis of the superior longitudinal sinus as the cause of the cortical changes. This assumption was subsequently re-emphasized by Schwartz[61] and more recently by Marburg and Casamajor.[62] But there is good reason to believe that venous occlusion cannot account for the occurrence of nodular cortical atrophy. The occurrence of this change well beyond the limits of cortical drainage by the superior longitudinal sinus and its afferents, its presence in so many cases in which venous thrombosis has not taken place, as well as the fundamental fact that, as a consequence of venous occlusion, the cortical changes are usually advanced and quite uniform, would seem to exclude this possibility.*

* *The writer has recently published a study dealing with venous thrombosis as an etiological factor in this and a variety of other cerebral lesions of early life* (Archives of Pediatrics, Vol. 56, p. 154 (April, 1939).

On the other hand, the idea that the pathogenesis of nodular atrophy rests on an arterial basis is not a new one. It is quite possible that Cruveilhier[1] who depicted so graphically this type of cortical lesion in an idiotic child, and who also studied a similar lesion in an elderly person presumably due to arteriosclerosis, may have entertained such a notion. At any rate, Spielmeyer[63] so concluded almost a full century later. Spatz[58] also noted this type of cortical alteration (Schizogyrie) in elderly people as a result of arteriosclerosis. With Lindenberg[64] he further observed occurrence in an obliterative but nonatheriosclerotic vascular disease. Meyer[65,66] likewise concluded that this type of atrophy of the cerebral cortex had an arterial genesis. The present writer[67] has recently pointed out the remarkable similarity between this lesion of early life and cortical changes of adults after partial arterial occlusion. The origin of cortical nodular atrophy in ischemia incident to an incomplete or transitory arterial occlusion now seems inescapable.

What is the primary cause of this arterial occlusion so early in life? Some writers (i.e., Hallervorden,[37] Clark and Linell[68]), have considered this obstruction to be embolic in nature. But from whence would an embolism come in antenatal life, during the process of delivery or in the early postnatal period when neither appropriate cardiac or pulmonary disease are ordinarily present? Meyer[65] considered thrombosis a possibility because of what he believed to be recanalization of previously thrombosed arteries. Yet in the great majority of these instances, evidence of arterial disease, including congenital vascular syphilis, was not forthcoming. The possibility of transitory arterial occlusion by compression has also been considered (Norman *et al*[10]). Since the location of nodular cortical atrophy usually occurs distant from sites where arteries are subject to compression, this seems to be a most unlikely cause.

It has long been recognized that asphyxia pallida at birth is characterized by a failure of both circulation and respiration. Gruenwald[69] and Norman *et al*[10] suggest that shock with circulatory failure under these circumstances may explain this evidence of arterial failure.

Is it possible that anoxemia, *per se*, is responsible for arterial spasm that results ultimately in a nodular atrophy? This actually seems to be the case. Such a conclusion is supported by an interest-

ing case reported by Meyer.[30] Two men had been asphyxiated by gases resulting from an explosion of blasting charges in a stone quarry. Both survived for many years but with lowered intellectual levels. On the death of one of them some 16 years later, the cerebral cortex was found to have undergone a widespread nodular atrophy. In other instances of severe anoxia with prolonged survival, irregular atrophy of the cortex has been noted (Courville, Sanchez-Perez and Anyes [1953]).[31]

This suggestion of anoxemia as the precipitating cause of nodular atrophy points to the birth process as the most likely time of its precipitation. One cannot conclude however that the natal period is the only time that causative circulatory disorders occur. It is certainly possible that vascular conditions of inflammatory nature do take place in early infancy and can result in certain isolated and unilateral cortical lesions. The present writer also believes that similar disturbances in the circulation of the fetal brain can take place *in utero*. This is suggested by the occurrence of already well developed lesions in the brains of infants who survive but a short time. This is also suggested in case of nodular cortical atrophy superimposed on congenital aberrations in the cortical pattern.

Primary versus Secondary Congenital Malformations of the Cerebral Cortex.—There are certain alterations in the size (pachy—or macrogyria, microgyria) as well as in the pattern of the cortical convolutions which appear to be the result of disturbances in morphogenesis. Such alterations are characterized by their smooth contour and uniform structure. These characteristics stand out in contrast to the lesion here described. When this atrophy is finely nodular, one is made to wonder whether or not its essentially circulatory cause has also been initiated during intrauterine life. This superimposition of a secondary effect upon a so-called primary congenital lesion must be carefully evaluated in any rational interpretation of etiological factors.

Another aspect of the possible arterial genesis must be considered. Why is it that cortical changes which are characteristic of nodular atrophy occur so often within the distribution of the middle cerebral artery, much less so in the distribution of the anterior cerebral artery while almost never in that supplied by the posterior cerebral artery? The structures (cerebellum and brain stem) supplied by the vertebral system are very rarely affected in this man-

ner. This situation cannot be explained by a circulatory collapse or anoxemia alone, which conditions should exert a more uniform cortical change. It must be the result of some untoward influence exerted on the arterial tree or that portion of it, originating in the carotid system.* This influence is apparently able to bring about an incomplete or transitory ischemia which persists sufficiently long to result in focal cell death, leading to the irregular cortical atrophy here described. Embolism or thrombosis could explain this in part (ischemia with partial atrophy with formation of mushroom type of convolutional change). It would seem, however, that an irregular pattern of atrophy can be explained only by a marked degree of narrowing affecting in variable degrees and in different areas, the individual arteries and arterioles. This conclusion seems inevitable in the uniform absence of any sign of vascular disease.

Theory of Selective Susceptibility of Vessels in the Carotid Arterial Tree.—A study of the distribution of foci of microgyria in autopsy specimens as a review of similar cases reported in the literature, emphasizes several points: (1) The location of these areas of microgyria suggests a fairly well-defined pattern of distribution. (2) These areas are found particularly commonly in the dorso-lateral parieto-occipital, the frontal and central (frontoparietal) areas, the upper pre- and postcentral gyri and paracentral lobule (motor cortex supplying the lower extremities) and rarely in the medical occipital (visual cortex) region. (3) One or more areas in symmetrical positions in the two hemispheres are often similarly and simultaneously affected. (4) Such areas are usually found within the field of supply of the middle, less often of the anterior cerebral arteries which stem from the carotid system. (5) The areas of nodular atrophy may occupy zones of arterial supply either in whole or in part; when in part the atrophic convolution usually seems to correspond to a terminal branch of the artery. (6) Extremely rarely is the cortex of the temporal lobe or of the medial occipital cortex lobe affected by this alteration, areas which are supplied by the posterior cerebral artery commonly derived from the vertebral basilar system. (7) The individual arteries supplying these atrophic areas usually prove to be smaller in size than are those supplying normal areas of cortex.

*This raises the question whether a contraction of the carotid arteries by cord of the umbilical cord about the neck, or by undue pressure during delivery, or the injury of the sympathetic on the neck, may be an explanation of contraction of the carotid body or an impairment of the carotid circulation.

These facts seem to warrant certain tentative conclusions. It is clear that the arteries derived from the carotid system are infinitely more vulnerable to the noxious process responsible for nodular cortical atrophy and associated processes, than are those originating in the vertebral-basilar system. In the absence of disease in these arteries, the possibility that the causative ischemia is the result of vascular spasm seems quite likely. The tendency for nodular cortical atrophy to occur in certain specific areas also suggests that the arteries supplying these areas are more vulnerable to vasomotor stimuli than others.

How is one to account for the multiple, symmetrically placed, and simultaneously occurring foci of nodular cortical atrophy? It would be very difficult to explain this phenomenon on either an embolic or thrombotic basis. It does suggest that these symmetrical portions of the carotid system are *simultaneously susceptible* to some noxious stimulus. To satisfy these requirements, it is necessary to postulate a vasomotor mechanism whose control over the cerebral arteries (carotid system) is spatially and synchronously effective, although not always entirely identical from one individual to another. It is presumed that this mechanism is resident within the vasomotor center of the medulla oblongata. It is possible, of course, that anoxemia may have some direct effect on the arteries themselves as suggested by isolated or irregularly distributed lesions. It is also possible that anoxemia may also influence either one or both carotid bodies which are known to be highly susceptible to chemical variation. But to explain symmetrically located lesions one must conclude that, although each half of the center presumably controls the corresponding carotid system, communication between the two halves of the center makes possible a bilateral synchrony in the vasomotor activities of the upper cerebral cortex.

The apparent relation of this mechanism to the problem of anoxemia can now be elaborated. At various points in this study, it has been pointed out that while nodular cortical atrophy is quite precisely duplicated by regional ischemia (Courville[67]), it can also occur as a late residual of anoxemia (Meyer,[70] Courville, Sanchez-Perez and Amyes[71]). Moreover, the various associated lesions such as cortical-subcortical cysts, central demyelination and cyst formation, and necrosis of the lenticular nucleus have been found in the cortex, centrum, and basal ganglia of the cerebrum of indi-

viduals who have long survived a severe anoxic episode, likewise suggest that anoxemia lies at the root of the trouble. If these assumptions have been logically taken, it must now be concluded that anoxemia exerts a noxious influence on the vasomotor center of the brain which in turn provokes a pattern of vasospasms resulting in the types of nodular cortical atrophy here under consideration. A final deduction is that this noxious stimulus provided by anoxemia does not strike only once but there must be a prolonged continuation of this effect as indicated when a subacute lesion (softening) is added to a chronic one (atrophy). This situation the writer has long suspected from his studies of cerebral anoxia, both from a clinical and pathological viewpoint.

These conclusions all fit into the known facts regarding the end results of cerebral anoxia. The variability of the lesion-complexes so often present in these specimens, is thus easily accounted for, as is the case after cerebral anoxias of later life. Moreover, certain aspects of the individual lesions found at autopsy especially in very young infants, imply that the lesion is not a static but a kinetic one. This assumption is also in accord with observations on anoxic residuals of adult life when both clinical symptoms and signs as well as pathological changes indicate that the necrobiotic process set in motion by oxygen want does not end when the supply of this vital gas is once more established. Different stages of softening and gliosis in various portions of the infant brain eloquently testify to this fact.

SUMMARY AND CONCLUSIONS

This study is concerned with the precise cause and mechanism of production of nodular cortical atrophy ("mantle sclerosis") which is probably the most common and most conspicuous lesion in the brains of cerebral palsied children. Its basic lesion is an acquired type of microgyria, an irregularly shrunken segment of one or more cerebral convolutions. This condition has been recognized for well over a century but only in recent years has it come to be better understood in terms of its pathogenesis.

The brains of a group of 40 individuals palsied from early life were available for study. From a survey of the pertinent literature, as well as from an investigation of these specimens, it was found that the distribution of these lesions suggested ten different anatomic groupings, including its association with the closely related

lesion of porencephaly. Alterations in the cortex are commonly associated with changes in the underlying white matter and basal ganglia which give rise to variable lesion-complexes. The histological picture likewise follows a pattern which has also come to be recognized through its variability by a tendency to an irregularity of nerve cell loss as well as interstitial scarring.

As for the mechanism involved, it seems reasonably certain that nodular cortical atrophy is an effect of an arterial rather than a venous occlusion. Because there is, as a rule, no evidence of arterial disease or residuals of a previous occlusion, vasospasm seems the best way to account for the necessary ischemia. As the resultant lesions are found most commonly in the distribution of the middle cerebral artery, almost always within the distribution of the branches of the carotid system, it is believed that the vasospastic phenomena occur most often in this system. The bilateral and symmetrical location of the areas of atrophy further suggest that this abnormal stimulation comes from a dysfunction of the vasomotor center itself. Evidence is given herewith to the effect that anoxemia in its various forms in the antenatal, natal, or early postnatal period is a common if not the chief cause of the abnormal vasomotor stimulation. This accounts not only for the ultimate cause of nodular cortical atrophy, but also explains the not infrequent association with other lesions which are simultaneously the result of a second widespread process in the form of anoxemia.

Nodular cortical atrophy is therefore not an isolated disease but the result of an ischemic process. In case of individuals palsied from early life it may be the result of ischemia from a variety of causes but is probably most often precipitated by anoxemia at the time of birth.

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Wilms' Tumor in Children
Report of a Very Unusual Case

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Many previous reports have been made concerning the Origin and Management of Wilms' Tumors. Rusche[1] has reported an extensive study in 1951. Gross[2] in 1953 gave an outstanding review and experience, and made many significant contributions to current literature.

The cardinal points necessary to arrive at the most optimistic type of management in these cases are: 1) early diagnosis, best accomplished by accurate physical examination and especially abdominal palpation; 2) prompt complete nephrectomy; 3) adequate x-ray therapy pre-operatively; 4) careful repeated abdominal examinations and reoperation and removal of any recurrent tumor, with additional x-ray therapy post surgically. The prognosis has always been bad in Wilms' Tumors. However, the case reported here indicates what can be accomplished by following the cardinal points mentioned here.

CASE REPORT

The patient was a female age 4½ years when first seen on 5-27-47. The general past health had been good. She had had measles but, no serious illnesses. The chief positive finding was the presence of a large movable left sided abdominal mass. No urinary symptoms or findings were present. The case was referred on 6-6-47 to Dr. Robert Prentiss who did a complete urological study, including cystoscopy which confirmed the diagnosis of Embryonic Carcinoma of the left kidney (Wilms' Tumor). He advised deep x-ray therapy and if no metastases were present, surgical removal of the tumor. Deep x-ray therapy was given in adequate amounts and surgery was performed on August 8, 1947. X-ray therapy in adequate amounts was given post-operatively. Prentiss[3] has reported some of the aspects of this case in 1955. The patient was followed regularly

during the next five years with particular attention being paid to abdominal examinations. No evidence of any recurrence was present up to the examination of February 1952, at which time a mass about the size of an orange was palpated in the left abdomen. It must be noted here that the growth and development of the patient had been excellent and normal, so much in fact, that the parents had failed to report for examination in the period from August 1951 to February 1952. The patient was again referred to the Urologist who had performed the original surgery. The patient, at this time, was about 10 years of age. In February and March 1952 X-ray therapy to a total of 1950 r, air was given to the anterior abdominal wall. The original field was 12 x 10½ cm. in size which was subsequently reduced to 12 x 8 cm. From 3-12-52 through 3-28-52 a left abdominal field was given 2,000 r, air to a 12 x 7 cm. field. The technical factors in all cases were 250 KV.P., 15 ma, 0.5 mmcu plus 1.0 mmal added filtration, 50 cm. distance. The X-ray therapy reduced the mass in size greatly and was well tolerated. Surgery was performed on 5-15-52 with removal of a tumor which pathologically proved to be a Wilms' Tumor. Post operative X-ray therapy was used to the full safe dosage. There were complications following the second surgery requiring a cecostomy, following which the patient appeared well and normal in her growth and activity, and apparent full recovery occurred. During 1952 and 1953, the patient was well and was under regular observation.

On examination in January 1954 a fairly large mass was again detected in the left abdomen. The mass seemed to be fixed to the colon and abdominal wall and appeared to be retroperitoneal, also. After consultation with the Urologist, who had performed the previous surgery, and a general surgeon, Dr. Peter Crabtree, of San Diego[1] surgery was again agreed upon. And even though surgery seemed to offer a hopeless prognosis, surgery was done after preoperative X-ray therapy. The surgical procedure was difficult, the tumor being attached to the descending colon and being partially retro-peritoneal. Post operative X-ray therapy was carried out again to a maximum degree. Regular careful examinations, especially of the abdomen, have been consistently normal since 1954. In addition, normal development, adolescence and menstruation occurred. Since the age of 14 years the menstrual cycle has been normal. When last examined on 9-29-59 the patient was 17 years of age, weight 105¾ lbs., height 58¼". Physical examination

showed no recurrence of an abdominal mass. This was a period of 5 years and 8 months after her 3rd surgical procedure.

DISCUSSION

This case merits attention because of the multiple recurrences and recoveries thereafter, and because of the normal development and menstruation after so many repeated dosages of such intensive x-ray therapy. Also, this would seem to indicate that Wilms' Tumors may arise from multiple embryonal cell rests that become active at different periods, and that these recurrent tumors are actually not metatastic but new tumors. In dealing with the management of these tumors this probability should be kept in mind.

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Aminophenylpyridone, A New Mood-Stabilizing Drug*

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A major break-through in the research effort to eradicate mental disease was initiated several years ago with the introduction of a new form of drug therapy based on the concept of "tranquilization". Since then the drugs, which have come to be known as tranquilizers, have been employed in a wide variety of neuropsychiatric conditions both in adults and children. They are now well established as important means for bringing relief to emotionally labile children, the restless, tense, irritable, and aggressive children whose problems affect not only themselves and their families but often society at large.

In the past, little could be done for the majority of them. At present, even the most severely psychotic children are improved after a course of treatment with the phenothiazine derivatives or reserpine. Less severe conditions are brought under control by meprobamate and other ataractic agents. Thus Bender and Nichtern[1] report improvement in severely disturbed children treated with chlorpromazine, reserpine, and antihistaminics. And Litchfield[2] reports relief of anxiety and tension states in children treated with meprobamate.

Satisfactory as these results have been, the drugs continue to elicit side-effects of varying degrees of severity in a number of patients. To the problem confronting the physician who must provide relief without unnecessary discomfiture to his patients, tranquilizers have not provided a satisfactory answer. What is needed is a drug capable of stabilizing mood, yet free of concomitant, undesirable effects.

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It now appears that such a drug may have been uncovered in a new series of chemical compounds designated as aminophenylpyridones. One member of the series, 1-m-Aminophenyl-2-pyridone, has been given to more than 1000 patients to date. Cass,[3] reporting on nearly 100 patients at Harvard, found it effective in 80% of cases involving anxiety and tension states; side-effects were rare and generally inconsequential. Cantelmo,[4] obtained relief in over 90% of patients treated with aminophenylpyridone for a variety of neuropsychiatric disorders and, here again, no serious side-effects were encountered. These findings are in harmony with the results of pharmacological studies in which the drug was administered to animals of various species including the mouse, rat, guinea pig, rabbit, cat, dog, and monkey. In all species aminophenylpyridone was devoid of sedative-hypnotic activity. Moreover, in the mouse, rat, and dog the fundamentally non-toxic character of the drug has been repeatedly confirmed both in acute and chronic toxicity experiments.[5]

In monkeys with permanently implanted cerebral electrodes, aminophenylpyridone increased electrical thresholds and decreased duration of seizures evoked by stimulation of the motor cortex, thalamus, and septum. Other areas including the amygdala and hippocampus were not affected by the drug, suggesting that it had a limited area of activity.[6]

The present study of aminophenylpyridone was designed with a three-fold objective to determine: (1) whether it would bring relief to emotionally labile children; (2) whether side-effects were significantly less than with the ataractic drugs; (3) its safety as revealed by studies of blood and urine. The details of this study are presented in the following pages.

MATERIALS AND METHODS

A group of 118 maladjusted, emotionally labile children was studied over a period of six months. Of these only 75 reported to the clinic at sufficiently frequent intervals to be included in the study. A complete case history was obtained for each child, including a detailed account of the mother-child relationship. In our experience the effects of drug therapy in emotionally labile children can easily be vitiated by a mother's influence. The role of the mother in relation to her child was classified as either "growth fostering" or "growth constricting". Special psychiatric help was recommended for the latter group of mothers, since their fears or

anxieties markedly "constrict" the child, and their dominance and control often provide stumbling blocks in therapy.

The children selected for treatment ranged in age from 8 months to 16 years, as follows: 1, eight months, 1, one year, 2, two years, 2, three years, 2, four years, 7, five years, 8, six years, 5 seven years, 5, eight years, 7, nine years, and 35 in the 10 to 16 year age group. Fifty to 300 mgs. of aminophenylpyridone was administered in single doses or up to three times daily, depending on age and condition. In most instances, however, 100 mg. doses were ordered b.i.d. A control group of 33 patients received recommended doses of reference drugs including phenobarbital, meprobamate, chlorpromazine, and reserpine.

Each child was given a physical examination before, during, and after medication. Samples of blood and urine were taken at the same intervals and other tests were performed where indicated.

RESULTS

The results of experimental findings, summarized in Table 1, reveal that aminophenylpyridone provided relief in 96% of 75 cases. Less satisfactory results were obtained in the group treated with the reference drugs. Side effects were negligible after aminophenylpyridone and laboratory findings disclosed no abnormalities.

TABLE 1

Drug	Percent Improvement *Marked*	*Moderate*	*Slight*	*Total*
Aminophenylpyridone	32.0	49.3	14.7	96.0
Phenobarbital		11.1	11.1	22.2
Reserpine		—	33.3	33.3
Chlorpromazine			67.0	67.0
Meprobamate		16.7	25.0	41.7

CASE REPORTS

To illustrate the therapeutic effectiveness of aminophenylpyridone, five representative cases have been selected for presentation.

CASE 1. M.S., a 12-year-old boy adopted at the age of 24 weeks, was admitted to the clinic because of nervousness and irritability, lack of interest in school games, and outbursts of temper at home when his demands were not met. Phenobarbital failed to bring relief. Medication with aminophenylpyridone (100 mg. h.s. for two weeks) was started January 20, 1959. By February 8th

the child was more animated and less resentful answering questions, hence drug therapy was continued. One month later (3/10/59) he was markedly less irritable. The wild temper outbursts were suppressed, and he became more cooperative both at home and at school. There were no side-effects, and laboratory findings were within the normal range.

CASE 2. B.S., an extremely nervous 16-year-old girl, was interviewed January 17, 1959 because of a fixed idea of two years duration that she had a "pain in the throat". This patient's condition was diagnosed as prepsychosis with fixation of ideas. Aminophenylpyridone (200 mg. b.i.d.) was prescribed 1/17/59. Within one week (1/24/59) improvement was evident, e.g., she was quieter, her throat felt better and her spirits were elevated. The following week (1/31/59), improvement was more marked and the patient stated that she was sleeping better. Six weeks later (3/14/59) improvement had continued and she was kept on the drug. No side-effects appeared during the course of therapy, and the results of blood and urine studies revealed no significant changes.

CASE 3. I.G., an 11-year-old boy, was interviewed January 24, 1959 because of the following symptoms which had persisted for approximately one year: (1) slow coordination; (2) alternate constipation and diarrhea; (3) bouts of crying; (4) frequent urination; (5) phobia referable to the use of the hands.

Physical examination revealed a poorly nourished, under-developed child with an extremely thin chest wall. Weight was 55 lbs., and height, 52 inches. The child exhibited an emotional enuresis. Aminophenylpyridone therapy (100 mg. daily) was started 1/24/59, and continued for six weeks. By March 14, 1959 coordination was much improved, crying was less frequent, and enuresis occurred only in response to scolding. During the treatment period he gained 1½ pounds. No side-effects of any kind appeared and the results of blood and urine studies disclosed no significant changes attributable to the drug.

CASE 4. J.Q., a 9½-year-old boy, was admitted November 8, 1958 because he had been hyperactive, quarrelsome, and restless for a period of one year. His condition was diagnosed tentatively as a behavior problem and medication with aminophenylpyridone (100 mg. h.s.) was instituted. After taking the drug for two weeks

the child was calmer, more amenable, and less quarrelsome. There were no side-effects, and the results of blood and urine studies disclosed no abnormalities.

CASE 5. T.K., a 14-year-old girl, presented symptoms of premenstrual pain, headaches and a "tense" feeling, of one year's duration. Her condition was diagnosed as premenstrual anxiety and medication with aminophenylpyridone (300 mg. h.s.) was begun December 6, 1958, with instructions to take the drug for one week. At the end of this period the child was more relaxed, appeared more alert, and her headaches had disappeared. The dose of aminophenylpyridone was reduced to 100 mg. nightly. There were no side-effects and the results of blood and urine studies revealed no abnormalities.

SUMMARY AND CONCLUSIONS

Aminophenylpyridone provided relief with essentially no undesirable side-effects in 90% of 75 emotionally labile children. The drug was outstanding in cases involving enuresis, anxiety, tension and fear. In general, children showed an ability to concentrate more, became less demanding, less defiant, and more cooperative. Side-effects were minimal and generally inconsequential. We conclude that aminophenylpyridone is an effective mood stabilizing agent, safe enough for use in the practice of pediatrics.

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Pediatric Conference

THE BRONX PEDIATRIC SOCIETY

Thrombocytopenic Purpura Secondary to German Measles

Varicella Encephalitis (2 Cases)

Lebanon Hospital, New York, December 9, 1959

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GEORGE WEISS, M.D., F.A.A.P.**

EMANUEL APPELBAUM, M.D.***

DR. COHEN: Once again we are happy to present to you cases from the Pediatric Service of Lebanon Hospital. We hope that the program will be an interesting and illuminating one. We are going to deviate somewhat from our custom of having discussion at the end of the meeting and will have the discussion at the end of each case. The first is one of thrombocytopenic purpura secondary to German Measles. Dr. Lewis B. London.

DR. LONDON: Rubella is described in text books as a mild disease running a short and uneventful course. It has been considered advisable for young girls to acquire Rubella before the age of child-bearing even to the extent of deliberately exposing them to the disease. This practice is open to serious question in the light of severe complications following Rubella, particularly encephalitis and thrombocytopenia.

In May of this year, a 7 year old school girl developed a macular-papular rash on her face which spread to the trunk, back and extremities the following day. The posterior occipital and retro-auricular lymph nodes were enlarged. She was symptom and fever free. No therapy was prescribed. There was no history of purpura or abnormal bleeding in the family. The rash disappeared after three days. The day following disappearance of the rash, the

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temperature rose to 102°. That night the child had a profuse nose bleed which was partially controlled by packings. When seen in the morning, purpuric patches and petechiae were noted over the shoulders, arms, legs and buttocks. Bleeding was evident from the nares, retropharynx, buccal gingival tissues. By the time the child reached the hospital, bleeding from the vagina and gross hematuria were present. Liver and spleen were not palpable. Initial laboratory studies showed hemoglobin 10.7 gm., RBC 3,500,000, WBC 8,200, with 64% polys, 34% lymphocytes and 2% monocytes; blood platelets less than 20,000, bleeding time over 20 minutes. Prothrombin time was 14 seconds, prothrombin consumption time was reported as no prothrombin used in 15 seconds. The Coombs test was negative, heterophile antibody 1:16; sternal marrow studies myelocytes 10%, non-segmented polys 43%, segmented polys 3%, normoblasts 36%, erythroblasts 4%, lymphocytes 4%; megakaryocytes were seen without platelet formation. The urine was grossly bloody with innumerable RBC's and 2+ albumin. The child was given steroid and antibiotic therapy.

The following morning the hemoglobin fell to 9.5 gm. with 2,760,000 RBC's and 54,000 platelets. That afternoon the child passed tarry stools and vomited copious amounts of blood. The hemoglobin dropped to 5.5 gm., RBC's to 1,500,000 and platelets to 27,000. A transfusion of one unit of fresh blood was added to the ACTH, meticorten and antibiotic therapy. The following day, after a second pint of fresh blood, the hemoglobin rose to 9.8 gm. with 2,840,000 RBC's. On the 6th hospital day, the temperature, which had been ranging to 102° daily dropped to normal and remained so. The purpura cleared, urine and stool returned to normal, the hemoglobin had risen to 10.6 gm., RBC to 3,800,000 and platelets to 180,000 at the time of discharge from the hospital on the 14th day.

Examination six months later revealed a healthy girl who had suffered no recurrence of bleeding. The hemoglobin was 14 gm., RBC 4,400,000 and platelets 260,000.

Discussion

Hudson (1) in reporting two cases of thrombocytopenic purpura complicating measles, reviewed the literature. Of 22 cases following measles, there was a mortality of 22% due to bleeding into the brain, heart or kidneys.

Thrombocytopenic purpura complicating scarlatina, varicella

and infectious mononucleosis has been reported (2). In 1929, the first case of thrombocytopenic purpura following rubella was documented by Pitten and since then many have been reported. In all, 17 cases of thrombocytopenic purpura complicating German measles have been described, with two deaths due to cerebral hemorrhage. In a series of 21 cases of Rubella reported by Steen and Thorp (3), three were complicated by encephalitis, two by thrombocytopenic purpura. This incidence of serious complications suggests that an extremely virulent strain of virus had been the cause as has been seen in epidemics of poliomyelitis. In his report of three cases of thrombocytopenic purpura following rubella, Ackroyd (4) showed the platelet count to be low and the capillary fragility high in control cases of uncomplicated rubella. He concluded that variations in the susceptibility of the patient's tissues determine the degrees of increased capillary fragility and thrombocytopenia. Manifestations of purpura soon after the initial infection would indicate a high degree of tissue susceptibility. Purpura developing during the convalescence suggests an allergic basis, similar perhaps to the development of nephritis after streptococcal infections.

In summary,

1. Viral or bacterial infections, of any degree, may be followed by thrombocytopenic purpura. 2. The incidence or severity of thrombocytopenic purpura bears no relationship to the severity of the primary infection. 3. The interval between the onset of the primary infection and the appearance of purpura may vary between one and twenty-eight days. 4. In view of potential serious complications, rubella cannot be considered a harmless disease.

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DR. COHEN: Thank you, Dr. London. This interesting case is now open for discussion.

DR. GRAND: What was the time interval between the administration of steroids and the transfusion?

DR. LONDON: Steroids were started the day following the admission to the hospital. Forty units of ACTH were added to each of the transfusions which she received. It was then decreased to 10 units, and then to 5 units. The hemoglobin never dropped below

5 gm. and the red blood count was 1.5 million cells. She received sufficient blood with the transfusions.

DR. GRAND: Fanconi reported 17 cases of thrombocytopenic purpura with German measles and we asked him about transfusions and he was convinced that you don't have to rush in with transfusions that rapidly. These children are in the hospital and you use your transfusions at a point where you think it is most urgent and in better than 50% of the cases he presented they didn't have to have the transfusions at all. If this whole problem concerns antigen antibody reaction, I wonder if the treatment with steroids might answer the question.

DR. LEVY: Fanconi might be correct, but I would rather give the child a transfusion.

DR. COHEN: The danger is of a cerebral hemorrhage and we don't want to take a chance. Any other comments, Dr. London?

DR. LONDON: Although the incidence of this complication is quite rare, there are far more of them than have been documented. Dr. Carl Smith also said he had seen four during this past winter.

DR. MILLIKEN: Was any history of respiratory infection elicited prior to the onset of German measles?

Were any renal studies made six months after discharge from the hospital, such as blood urea, to make sure there were no complications following this condition? We know that anaphylactoid purpura has been reported as being followed by renal complications later.

DR. LONDON: There was no respiratory infection prior to the onset of German measles. We did no urea clearance tests on this child. She had a complete blood count, urinalysis and everything was entirely clear.

DR. GREENSTEIN: I don't think I quite caught the description, but was there a point made about the fact that there was no prothrombin consumption for 15 seconds? Is there any significance to this in relation to the failure of blood coagulation here?

DR. LONDON: In thrombocytopenia there is a platelet factor defect and because of defective thromboplastin generation, prothrombin is not consumed in normal amounts during the process of clotting.

DR. GOLOMB: Has Dr. London any exact statistics of cases of German measles and the development of purpura?

DR. LONDON: This is a very difficult question to answer since there are no available statistics.

DR. LAPIN: I didn't hear the report of the Coombs test. Had aspirin been given during the course of the German measles?

DR. LONDON: The Coombs test was negative. I saw her the very first day of the rash, and then three days later. She received no therapy whatsoever and no aspirin; and after all the symptoms had disappeared, the purpura appeared.

DR. LEVY: We had four cases of chickenpox followed by thrombocytopenic purpura, so I would question whether this is as rare as the literature would lead you to believe; we never reported our cases and Dr. Applebaum at Willard Parker had many cases. I had one case where we had post-German measles encephalitis with a consequent hemiplegia.

DR. LAPIN: Had this child an exposure to German measles or was this just a clinical diagnosis? Perhaps the rubella-like symptoms were part of a thrombocytopenic purpura.

DR. LONDON: With regard to the German measles exposure, this girl had two siblings, each of whom had German measles and the other children in the neighborhood had German measles. She presented what appeared to be a typical macular rash, pinkish, covering all of her body and there were enlarged post auricular nodes.

DR. COHEN: Rubella is a difficult diagnosis to make at any time. Incidentally, some of you may have read a recent article in the New England Medical Journal on Rubella. They had a terrific epidemic of German measles in Taiwan, and 1,000,000 out of a population of 10 million contracted the disease. Various methods of prevention were tried, and it was found that 2 cc. of gamma globulin given soon after exposure to the disease was valueless. They too found, as Krugman & Ward did, that with pregnant women 20 cc. gamma globulin was necessary to prevent the disease. They also used a convalescent-phase gamma globulin, as much as 5 cc. in boys (25 Kg.), and in one school they were able to prevent the disease when cases occurring during the first week after inoculation are excluded. Recently, I saw a very severe case of encephalitis following German measles; nevertheless, I still advocate exposing unmarried females to Rubella.

DR. APPLEBAUM: I do recall that we had such cases as have been presented, at Willard Parker Hospital but I have no statistical information. With reference to encephalitis, again I have no statistical information but the incidence is lower than in other infections. However, we have had quite a number of cases of encephalitis.

DR. ALTMAN: Have any studies been made for Echo virus?

DR. LONDON: No such studies were made.

DR. EISENOFF: I was interested in Dr. Golomb's question whether it is worth exposing young girls to German measles. Knowing the possibility of complications as against the mother's contracting German measles and then giving birth to a child with some congenital anomalies, I think that is a very important question and I don't think we have settled it here. Offhand I would say that the complications of German measles are very rare, whereas a child born with a congenital anomaly is something that one has to consider. Under the circumstances, I think it is more than worthwhile exposing the unmarried female to German measles. Only recently I received a communication from London from Professor Jackson, who stated that not alone are there immediate evidences of sequelae in the new-born child, but if you watch these children born of mothers who contracted German measles in the first trimester, a good percentage develop something that we were unaware of. They develop deafness in one or both ears, to a greater or lesser extent so that children born of mothers with German measles must be observed for the possibility of this and other sequelae.

DR. COHEN: Dr. George Weiss will now present two cases of varicella encephalitis.

DR. WEISS: Varicella, whether mild or severe, has usually been considered a self-limited disease and with few complications. That it may not be so innocuous a disease, is shown by recent experience.

A case of myositis complicating chickenpox was seen not too long ago at Lebanon Hospital and in a period of about one month, two cases of encephalitis associated with varicella were observed and are the subject of this report.

M. C., a twelve year old white male, was admitted to Lebanon Hospital on February 16, 1959. The present illness began 8 days previously with a temperature of 103° and a chickenpox eruption.

Four days later he began to vomit and two days prior to admission he became listless, apathetic, vomited repeatedly and became dizzy if he attempted to stand.

Family History: Father and mother are alive and well. Two siblings are alive and well. One sibling had chickenpox three weeks previously.

Past History: Normal birth and developmental history. Measles at five years. Had always been an alert, energetic child. He was bright and in an accelerated class.

Physical examination revealed a well developed, twelve year old boy, who was very listless and lethargic. He attempted to cooperate but responses were very slow. *Neurological*: stiffness of spine; suggestive Brudzinski; deep tendon and superficial reflexes were normal. No abnormal reflexes were present. The cranial nerves were intact. A fading varicella rash was present. Temperature curve was normal except for a rise to 101° on the fifth hospital day. Complete blood count showed hemoglobin 14.8 gm., WBC 8,700, polys 68%, basophiles 8%, lymphocytes 20%, eosinophiles 4%. Spinal tap on admission showed clear fluid, 9 cells. Pandy was negative, Protein 65 mg.%; Sugar 70 mg.%. *Blood chemistry*: urea nitrogen 17 mg.%, CO_2 22 meq.

For the next five days the boy was stuporous, apathetic and refused food. On the second hospital day he developed lateral nystagmus, slow scanning speech, unsteady hand movements and past-pointing. At this time he was seen in consultation with Dr. Applebaum, who concurred in the diagnosis of encephalitis complicating varicella, cerebellar in type.

By the sixth hospital day he began to show some improvement in his condition. The defects in his speech, hand movements and apathy began to lessen but at a slow pace.

By the 18th hospital day, he was much brighter. However, he walked unsteadily, with an ataxic gait.

By the 20th hospital day, speech was normal and he was mentally alert. Past-pointing was still present and movements were less awkward. He was discharged for further observations at home.

Treatment was supportive throughout, consisting of ACTH and

intravenous fluids during the first two days of hospitalization. Blood for viral studies was taken but not reported.

The second case is that of E. G., an 11 year old white male, admitted to Lebanon Hospital on March 25, 1959, ten days after the onset of a mild attack of varicella. For three days prior to admission, the boy vomited repeatedly, complained of headache, and was drowsy most of the time.

Temperature during the first few days in the hospital was normal, blood pressure 140/120. Examination revealed a fading varicella rash, stiffness of the spine, past-pointing (finger to nose and heel to knee). There was weakness of all the extremities. The deep tendon and superficial reflexes were absent. Spinal tap on admission showed a clear fluid under a pressure of 180 mm. of water. There were 8 cells, positive Pandy, protein 229 mg.%, sugar 87 mg.%. Complete blood count showed hemoglobin 13.1 gm., white blood cells 11,400 polys 26%, basophiles 4%, lymphocytes 20%, sedimentation rate 12 mm. Urinalysis revealed specific gravity of 1.018, 5-6 white blood cells, no albumin and acetone, urea 10 mg. The Mantoux was negative.

On the third hospital day he developed nasal speech in addition to the inability to move any of his extremities. He was seen at that time by Dr. Applebaum, who found him apathetic. There was generalized symmetrical paresis of the torso and extremities. The deep tendon and superficial reflexes were absent. There was minimal left facial and palatal paresis and modern nuchal rigidity and positive Brudzinski and Kernig's sign. The impression was that the clinical picture is that of varicella encephalitis associated with a Guillain Barre syndrome.

On the fifth hospital day he developed parasthesia of the fingers and pains in the back. The blood pressure was 145/120. The fluid intake to output varied in the ratio of 2-3:1. He was placed on serpasil (.2 mg. t.i.d.) and diuril (250 mg. b.i.d.) in addition to the ACTH which had been started the previous day. Over the next few days he developed difficulty in swallowing along with aphonia. He appeared critically ill and the question of using a mechanical respirator was considered at this time. Blood pressure remained at a high level of 170/150. There were signs of congestion at the left base. Antibiotics were given and postural drainage tried.

On the ninth hospital day, however, the temperature, which

had been up to 101.4°, came down to normal and he seemed slightly improved. He was able to move his head, and by the 13th hospital day he was able to move the upper extremities. Speech became less nasal. From this point on there was gradual return of function to the extremities and of normal reflexes. The hypertension gradually subsided to 90/60 at the time of discharge on the 25th hospital day.

Viral studies for blood were negative in 1:4 dilution for herpes simplex on March 26 and April 7, 1959. Blood chemistry showed: total protein 7.0 gm., albumin 4.2 gm., globulin 2.8 gm., urea 12 mg.%, on April 10, 1959. Electrocardiogram on April 9, 1959, indicated partial block with non-specific T wave changes, in V_1, V_2 and V_3.

The treatment consisted of antibiotics, ACTH, and intravenous fluids until such time as the patient was able to manage fluids orally.

DISCUSSION

Encephalitic manifestations may occur in any of the exanthemata. The incidence in measles is 1:600-1000, rubella 1:6000, smallpox 1:7000 and less common in the case of chickenpox according to reports.

All of these are considered as a post-infectious type of encephalitis. The pathology is generally considered to be a demyelination of the white matter of the cortex, basal ganglia or cord in varying intensity. An occasional case has failed to show this demyelination on histological study. However, the number of studies on autopsy material has been very few and permits of differences of opinion in regard to the pathology of varicella encephalitis.

The etiology of varicella encephalitis is unknown. Several views have been proposed: (1) there is a direct invasion by the varicella virus of the central nervous system; (2) there is an allergic response of the nerve tissue to the virus; (3) the varicella virus activates an unknown, dormant virus in the central nervous system.

Clinical findings: The signs and symptoms are related to the portion of the nervous system that is most intensely damaged and not to the severity of the disease itself.

In some cases there are signs and symptoms of generalized involvement but more commonly one or more portions of the nervous system suffer the brunt of the damage, resulting in various, fairly

clear cut syndromes that are meningeal, encephalitic, brain stem, cerebellar, spinal cord or neuritic in type.

Symptoms of involvement of the meninges, headaches, stiffness of the neck and drowsiness are common early in the course of all types. There may be further progression of symptoms in some; in others these may be followed by evidence of cerebral damage. In the encephalitic form there may be convulsions, stupor, coma, hemiplegia, aphasia or other signs of focal cerebral involvement. Cranial nerve palsies or signs of cerebellar dysfunction predominate in a few cases. In some it may take the form of damage to the spinal cord, such as a transverse myelitis, a Brown-Séquard lesion. Peripheral nerve involvement is rare in the encephalomyelitides complicating the exanthemata but it may occur.

Laboratory data: Cerebro-spinal fluid is clear; pressure is usually normal but may be slightly elevated. Cell count may range from 0 to 250 cells with predominance of lymphocytes. Protein content is normal or elevated (35-150 mg.%). Sugar and chlorides are usually normal.

Mortality statistics vary in different reported series ranging from 5-11% of fatalities. The prognosis is favorable in the majority of cases but each individual case must be given a guarded outlook. Aside from the fatal cases, a goodly percentage of the cases may have residuals and also some changes in the patient's status may occur with the passage of time following recovery from the acute phase of the illness, such as paresis, personality change, blindness and epilepsy.

There is no specific therapy available. Although there is no conclusive evidence of their value, steroids may be tried. They may prevent edema by decreasing capillary permeability and possibly early gliosis. Several studies on animals have shown that experimental demyelinating encephalomyelitis can be suppressed by the use of ACTH or steroids.

In conclusion, two cases of varicella encephalitis have been presented, one of which had a very stormy course, and whose outcome as to survival appeared doubtful at one time. The long term outlook for both cases can be best determined after a lapse of more time, a period of three years in some cases.

DR. COHEN: Thank you, Dr. Weiss. We are very fortunate in having with us this evening one of our good friends who is well known to this Society. He has come to speak to us and discuss these

cases, both of which he saw in consultation. Dr. Emanuel Appelbaum.

DR. APPELBAUM: Mr. Chairman, Members of the Society. Dr. Weiss has already covered the subject so comprehensively that there is very little for me to say. But I would like to emphasize some of the things he pointed out and for that reason I have brought some slides with me.

Actually the incidence figures shown are relatively high since the patients admitted to the hospital are quite likely to be very severe cases and undoubtedly show a higher incidence. I think the incidence of measles encephalitis is very much lower, closer to 4% and perhaps even lower; and the incidence of varicella encephalitis is still lower. This slide has its value in showing the relative incidence of the three forms of encephalitis.

Now with respect to the correlation of the time of onset of the encephalitis in relation to the first apearance of the varicella rash, the majority of the cases occur between three and eight post-eruption days. A case may occasionally occur on the same day and we have had cases occurring two or three days prior to the onset of the varicella as happens also in other forms of infection, like measles and rubella. On rare occasions a case will occur as late as three weeks and even later than three weeks after the onset of the rash. However, by and large, the cases occur during the first week of the post-eruption phase.

Dr. Weiss mentioned pathology. The pathology is a demyelinating form of encephalitis, but in most cases it is not as severe as it is in measles encephalitis. Most areas show a scant perivascular infiltration. Demyelination and edema, are seen. It is a demyelinating form of encephalitis even as measles is, but it is much less extensive and a much less severe form of encephalitis than the form seen with measles.

Now with respect to the spinal fluid, as shown by one of the cases here, the cell count may be quite normal but in the majority of cases there is a moderate pleocytosis, lymphocytic in character. In some cases there is a polynuclear predominance and, later on, the shift is to the lymphocytes. If you do more than one spinal tap, the pleocytosis does change towards the lymphocytic preponderance. That applies to the other forms of myelinitis. In many cases there is only a moderate increase but sometimes the increase is as high as three dozen cells. Now, with respect to the protein, here too the

protein is generally moderately increased. At times it is within the normal range but there are instances where the proteins are quite elevated as demonstrated by the second case where it was over 200 mg.%. Sugar is usually normal but occasionally it may be high and on rare occasions depressed, below normal. It is not the persistent depression of the sugar but a transitory depression of the sugar content which may occur early and that can cause a great deal of confusion if only a single spinal tap is performed, especially if the predominant cells are polys or lymphocytes.

Now, with respect to the symptomatology. Dr. Weiss enumerated most of the important symptoms by and large and I would say that most of the cases of varicella encephalitis are milder than measles encephalitis but one does run into cases that are quite severe, as with bulbar manifestations, as presented by the second case. Most show meningeal signs with the usual headache and nuchal rigidity. Any change in sensorium is common, although every now and then it happens that an occasional patient has a clear mental state. Some are perfectly lucid right through the entire illness. In the majority there is a change in the sensorium; stupor is not common, only lethargy or irritability, and that is about all. Delirium is quite rare. Motor changes and other cranial nerve involvements are certainly not rare.

I want to emphasize changes in speech of two types; of aphasia or speech disorder, or dysarthria. These patients are not able to enunciate or pronounce the words. This was true of one of the patients presented, who showed dysarthria. Another symptom that deserves emphasis is ataxia and other cerebellar phenomena. It is quite unique that in varicella, a very high percentage manifest cerebellar phenomena. Both patients showed evidence of cerebellar involvement. That has been the experience also of other workers that these patients show a high percentage of varying cerebellar manifestations, including ataxia. The paresis may be of the flaccid or spastic type and as demonstrated by one of the patients here, it may be in the form of ataxia. It may occur in any form of encephalitis. It may involve the central nervous system, the roots and even the peripheral nerves. The second patient showed a very classical picture of this in addition to the brain stem involvement and symmetrical peripheral neuropathy of the flaccid type which returned to normal in a short time and a facial paralysis which made for quite a classical syndrome.

Now with respect to the outcome of these cases—what is the

prognosis? The prognosis is generally better than in measles encephalitis. In a group of 56 patients, studied at the time, 43 or 77% were discharged from the hospital. The hospital stay is generally between two or three weeks on an average—the measles cases remain much longer, double if not more than the varicella cases. At the time of discharge from the hospital, the majority of the cases were free from any obvious neurological residua as far as we could make out by careful examination. About 10 patients, or 17%, did show definite neurologic residua including paresis, dysarthria, ataxia and incoordination. Furthermore, the fatality rate of 5% is lower than that in measles. In this group three of the patients died. Two of the fatal cases had pneumonia as well, and varicella pneumonia is notoriously a very serious disease which often proves fatal and is worse in adults than in children.

It is also interesting to note what happens to these patients when they are followed later on. We have followed them for a period ranging from one to ten years. In this group of twenty patients—we have had more since then—who were discharged without residua, later on two developed sequelae. One of the patients developed convulsions about two years later and another patient had definitely very serious personality changes noted within six months after discharge from the hospital. On the other hand, it is gratifying to note that on occasion patients discharged with residua may change too. Of eight patients who had residua at the time of discharge, six remained with the residua at the time of the follow-up. Dr. Weiss touched upon them, personality changes, mental retardation, paresis, etc. and transverse myelitis. It is interesting to note that two of the patients who had these and other changes later on, showed definite clearing. One of these patients was seen about two years later and the speech difficulty had cleared entirely. His speech had become entirely and perfectly normal. Another patient was seen four years after discharge with a facial paresis, and the paresis had cleared totally. Also, a number of cases of ataxia cleared, spastic state cleared and paresis cleared so that with the passage of time the condition of the patient may change and may improve. In the majority of the patients, the pattern of the patient's state is established at the time of discharge, but nonetheless, the situation may change with the passing of time and therefore one should be guarded with the prognosis. One should not be too optimistic, nor too pessimistic either!

DR. COHEN: Thank you very much, Dr. Applebaum.

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